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Short communication

MEDULLARY SEROTONERGIC NEURONS ARE INSENSITIVE TO 5-MEODMT AND LSD

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A comparison was made of the effects of 5-MeoDMT or LSD on serotonergic unit activity in the dorsal raphe nucleus (DRN) and nucleus raphe pallidus (NRP) of freely moving cats. NRP neurons were substantially less responsive than DRN neurons to both drugs. NRP neurons were unresponsive to behaviorally effective low doses of these drugs whereas the activity of DRN neurons was strongly depressed. These data are discussed in terms of autoregulatory control of serotonergic neurons.

Dorsal raphe nucleus Freely moving cats Hallucinogenic drugs Nucleus raphe pallidus Raphe unit activity Serotonergic neurons

1. Introduction

Serotonergic neurons within the dorsal raphe nucleus (DRN) of anesthetized rats and freely moving cats are distinguished from other neurons by certain characteristics including a slow and regular discharge pattern (for reviews see Aghajanian and Wang, 1978; Jacobs et al., 1981). In addition to their distinctive firing pattern, the activity of these neurons is potently and selectively depressed by either systemic administration or direct iontophoretic application of serotonergic agonists such as LSD (Aghajanian et al., 1968, 1972; Trulson et al., 1981) or 5-methoxy-*N*, *N*-dimethyltryptamine (5-MeoDMT) (DeMontigny and Aghajanian, 1977; Trulson and Jacobs, 1979). These inhibitory responses appear to result from an action of these drugs upon receptors located on serotonergic cell bodies, presumably autoreceptors (De Montigny and Aghajanian, 1979; Rogawski and Aghajanian, 1981).

We recently extended our studies of serotonergic neurons in freely moving cats to include those within the medullary nucleus raphe pallidus (NRP) (Heym et al., 1981). During the course of that investigation we noted that serotonergic NRP neurons appeared to be less responsive to systemic administration of 5-MeoDMT than what had been reported previously for serotonergic neurons in the DRN (Trulson and Jacobs, 1979). We now have explored this question in more detail by examining the effects of a low or high dose of 5-MeoDMT on NRP unit activity and extending this analysis to include a single dose of LSD. In this report we directly compare these effects on NRP unit activity with the responses of DRN serotonergic neurons to the same drug treatments.

2. Materials and methods

Fourteen adult female cats (2.4–3.2 kg) were anesthetized with pentobarbital (35 mg/kg, i.p.) and prepared for chronic single unit recording using a procedure that has been described in detail previously (Trulson et al., 1981). Briefly, two microelectrode bundles, each consisting of 6 flexi-

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ble insulated nichrome wires (3 each of 32 μm and 64 μm diam.) were stereotaxically implanted above either the NRP at an angle of 15° behind the vertical, or the DRN at an angle of 45° behind the vertical. Stereotaxic coordinates for the initial placement of the anterior bundles were P 9.5, L 0.0, H −7.5 for the NRP, and P 1.5, L 0.0, H +1.0 for the DRN. The microelectrode bundles were attached to a mechanical microdrive in order to advance them gradually through the brain.

Serotonergic neurons of the NRP and DRN were identified initially by their characteristic slow, regular discharge and pronounced decrease in firing rate during REM sleep (Heym et al., 1981; Jacobs et al., 1981). After obtaining 10 to 15 min of quiet waking baseline activity, animals were administered either saline (0.5 ml/kg, i.p.), 5-MeoDMT (50 or 250 μg/kg, i.m.), or d-LSD (50 μg/kg, i.p.). Recordings then were continued for up to 2 h post-drug. The baseline firing rate was calculated for each unit by taking the mean of six consecutive 10 sec time samples during pre-drug quiet waking. A post-drug firing rate was calculated for each unit in a similar manner using time samples from the period of maximal change in unit activity. Drug-induced changes in the firing rates of individual units were considered significant ($P < 0.05$) if a cell's post-drug firing rate was outside of the 95% confidence interval for the same cell's pre-drug baseline firing rate. The post-drug firing rate of each unit then was expressed as a percentage of its baseline firing rate and a group mean percent of baseline was calculated for each drug treatment (including saline) from the individual unit data. Differences between the effects of the drug treatments were evaluated for both NRP and DRN units using a one way analysis of variance coupled with the Newman–Keuls test. Differences between the responses of NRP units and those of DRN units to the same drug treatment were assessed using two tailed *t*-tests. Recording sites were located histologically utilizing a technique which has been described previously (Trulson et al., 1981).

3. Results

14 NRP neurons and 22 DRN cells initially were identified as serotonergic by their slow and regular discharge pattern. Histological examination revealed that all of these neurons were located within 500 μm of the midline in either the NRP or DRN. The mean baseline firing rate of NRP serotonergic neurons was significantly higher than the baseline firing rate of DRN serotonergic neu-

TABLE I

Responses of serotonergic neurons in either the dorsal raphe nucleus (DRN) or nucleus raphe pallidus (NRP) to systemic administration of 5-MeoDMT or LSD. 1-min samples of post-drug unit activity during the time when activity showed a maximal change, i.e. during the peak drug effect, were expressed as a percentage of pre-drug baseline activity. The number of cells which were significantly increased (↑) or decreased (↓), or unchanged (–) is listed for each drug treatment.

Drug	Dose (μg/kg)	Dorsal raphe nucleus					Nucleus raphe pallidus				
		n	% of baseline [1] firing rate	No. of cells showing			n	% of baseline [1] firing rate	No. of cells showing		
				↑	↓	–			↑	↓	–
Saline	–	5	100.2 ± 2.9	0	0	5	4	100.7 ± 2.2	0	0	4
5-MEoDMT	50	4	33.0 ± 12.1 [2]	0	4	0	7	84.0 ± 5.5 [3]	1	5	1
	250	8	0.0 ± 0.0 [2]	0	8	0	8	18.3 ± 6.0 [2,3]	0	8	0
LSD	50	8	49.2 ± 6.3 [2,4]	0	8	0	7	91.6 ± 10.0 [3]	2	5	0

[1] Mean ± S.E.M.

[2] Significantly different from saline, $P < 0.05$ (Newman–Keuls test).

[3] Significantly different from dorsal raphe nucleus, $P < 0.01$ (two tailed *t*-test).

[4] Value is calculated from a subsample of neurons previously reported in Trulson et al. (1981).

rons (3.94 ± 0.49 (S.E.M.) versus 2.79 ± 0.24 spikes/sec; $P < 0.05$, two tailed t-test). The higher discharge rate of NRP units is in accord with our previous finding that NRP serotonergic neurons have faster firing rates than serotonergic neurons of the DRN across all states (Heym et al., 1981).

Table 1 summarizes the effects of saline, 5-MeoDMT, or LSD injections on the activity of both NRP and DRN units. Administration of either 5-MeoDMT or LSD elicited characteristic behavioral responses which have been detailed previously (Trulson and Jacobs, 1979; Trulson et al., 1981). DRN unit activity was significantly depressed by both 50 and 250 μg/kg 5-MeoDMT and by 50 μg/kg LSD when compared to the saline control. Both doses of 5-MeoDMT significantly inhibited the activity of all DRN serotonergic cells tested. The 250 μg/kg dose completely inhibited every DRN unit examined. Following administration of this dose, the activity of DRN units began to slow within 5 min and complete inhibition always was attained within 15 min post-injection. Recovery of activity began at 30 to 45 min post-drug and usually was complete by 90 min after injection. The time course of inhibition of DRN unit activity after administration of 50 μg/kg 5-MeoDMT was similar except that recovery to baseline was faster, usually complete by 60 min post-drug. However, the magnitude of the maximal inhibition of DRN units produced by this dose was significantly less than after the 250 μg/kg dose. Injection of 50 μg/kg LSD resulted in a mean reduction of DRN unit activity to approximately 50% of baseline and the firing rate of every DRN serotonergic cell tested was significantly reduced. DRN unit activity usually began to slow within 5 to 10 min after LSD administration and the maximal inhibition was attained at 45 to 60 min post-injection. Activity usually recovered to within 20% of baseline by 2 h post-drug.

In contrast to the strong inhibition of DRN unit activity produced by LSD and both doses of 5-MeoDMT, NRP unit activity was relatively unresponsive to 50 μg/kg of either LSD or 5-MeoDMT, but was strongly inhibited by 250 μg/kg 5-MeoDMT. 50 μg/kg of either LSD or 5-MeoDMT, although behaviorally effective, resulted in a mean change of NRP unit activity to only 91.6 and 84.0% of baseline, respectively. However, these responses were not significantly different from the saline control and, although a decrease in firing rate was the predominant response, the effects on individual NRP units were mixed (table 1). The response of NRP serotonergic neurons to 50 μg/kg of either LSD or 5-MeoDMT was significantly less than the responses of DRN serotonergic cells ($P < 0.01$, two tailed t-test). Only 250 μg/kg 5-MeoDMT reduced NRP unit activity to a level, 18.3% of baseline, that was significantly different from the saline control. The firing rate of every NRP unit tested was significantly decreased by this higher dose of 5-MeoDMT. However, the magnitude of the depression of NRP unit activity produced by 250 μg/kg 5-MeoDMT was significantly less than the inhibition of DRN unit activity produced by the same treatment ($P < 0.01$, two tailed t-test). In general, the rapid time course of the inhibition of NRP unit activity by 250 μg/kg 5-MeoDMT was comparable to that of the depression of DRN unit activity produced by the same dose of this drug.

4. Discussion

The results of the present study demonstrate that, in freely moving cats, serotonergic neurons of the NRP are markedly less responsive than DRN serotonergic neurons to systemic administration of 5-MeoDMT or LSD, compounds which can act as serotonergic agonists. A low, but behaviorally effective, dose of either 5-MeoDMT or LSD did not significantly alter NRP unit activity while these same treatments produced a strong inhibition of DRN unit activity. A higher dose of 5-MeoDMT depressed both NRP and DRN unit activity, however, the degree of inhibition of DRN unit activity was significantly greater. Thus, the response of serotonergic neurons to systemically administered serotonergic agonists does not appear to be uniform throughout the brain, but instead may show substantial variation depending upon the nucleus in which the cells are located.

The differential pharmacological responses of NRP and DRN units may be an indication that serotonergic neurons of the NRP are actually less

sensitive to serotonergic agonists than are their counterparts in the DRN. The relative insensitivity of NRP neurons may be due to a lower affinity of serotonergic agonists for presynaptic autoreceptors and/or a lower density of receptor sites. Alternatively, there may be a difference in drug distribution to the DRN and NRP so that a systemically administered compound is less available to NRP neurons. This latter interpretation seems unlikely since, in the anesthetized rat, presumed serotonergic neurons in the more caudal brainstem raphe nuclei, including the NRP, have been found to be much less responsive than serotonergic neurons of the midbrain raphe nuclei to direct iontophoretic application of serotonin or LSD, as well as i.v. administration of LSD in high doses (Haigler, 1978).

Further work involving more detailed iontophoretic studies and receptor binding techniques will be necessary to elucidate any receptor differences that may account for the differential sensitivity of NRP and DRN serotonergic neurons to serotonergic agonists. Since autoreceptors may play an important role in the regulation of serotonergic neuronal activity (Aghajanian and Wang, 1978), autoreceptor differences may result in varying degrees of regulatory control for NRP and DRN neurons. Consistent with this hypothesis, we recently have found that, for both NRP and DRN neurons in freely moving cats, a significantly inverse correlation exists between firing rate during waking and the magnitude of inhibition produced by 5-MeoDMT or LSD (Heym and Jacobs, unpublished observations). Therefore, the higher activity of NRP serotonergic neurons, compared to those of the DRN, across all behavioral states (Heym et al., 1981) may be a reflection of a difference in autoregulatory control.

Finally, these data suggest that mesencephalic serotonergic neurons which project to the forebrain may be more importantly involved in hallucinogenesis than medullary serotonergic neurons which project to the spinal cord.

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